# The DEPOSEIN - how meaningful was the benefit from intrathecal chemotherapy?

Le Rhun, Emilie ; Weller, Michael ; Le Deley, Marie Cecile

DOI: https://doi.org/10.1093/neuonc/noaa195

The DEPOSEIN – how meaningful was the benefit from intrathecal chemotherapy?

We appreciate the interest of Shivaprasad and colleagues in the DEPOSEIN trial [1]. Our colleagues (i) address imbalances between study groups summarized in their Table 1 and (ii) challenge the clinical relevance of the differences in outcome between groups.

Imbalances in study arms are inevitable in a relatively small study and in a highly complex clinical setting such as leptomeningeal metastasis. As stated in the CONSORT statement [2], any differences in baseline characteristics are, however, the result of chance rather than bias. As recommended, we have not provided significance tests of baseline differences, which would only assess the probability that observed baseline differences could have occurred by chance. In the current context, the only significant difference would concern the HER2 status (p=0.045), as the other p-values are p=0.20 for “poor differentiation”, p=0.42 for “T1-T3” versus “T4”, p=0.50 for “N0-N1” versus “N2-N3”, p=0.25 for “prior CNS radiotherapy”, p=0.13 for “brain metastasis”, p=0.35 for ECOG 0 versus 1 versus 2-3 and p=0.14 for neurological deficit “no” versus “major” versus “other”. Also, imbalances *per se* are not a main concern unless there is clear evidence of imbalance of a prognostic factor favoring one study group. This remains to be clarified for HER2 status for which the imbalance was also moderate at best, but preliminary evidence suggests that this imbalance favored the control arm [3].

Our colleagues suspect “flawed concealment of the allocation sequence”. The randomization list was not known by the investigators, but only by the sponsor’s Research Unit staff, which is certified ISO9001 and has been successfully audited by the French regulatory authority. Lastly, we performed a prespecified sensitivity

analysis, adjusting for potential confounding factors (ECOG performance status at leptomeningeal metastasis diagnosis, number of prior lines of systemic treatment, HER-2 status, and positivity of CSF cytology at leptomeningeal metastasis at diagnosis). The estimated magnitude of treatment effect was even larger in the adjusted analysis.

We had rather extensively discussed the limitations of the DEPOSEIN trial in the original report. Yet, it remains the only randomized trial in this setting for many years. We had acknowledged that the benefit in progression-free survival may be of moderate overall clinical relevance, but leptomeningeal metastasis-related progression-free survival remains a meaningful outcome parameter to assess benefit of a local treatment, and quality of life assessment supported our conclusion. Furthermore, we believe that our results support continued exploration of the subarachnoid space as an important compartment for therapeutic intervention, using better drugs than cytarabine in molecularly enriched patient populations.

Finally, clinical trials should be judged by the state of the science and knowledge when they were designed and conducted. Undoubtedly, future trials in leptomeningeal metastasis might benefit from the challenges and shortcomings experienced during the conduct and analysis of DEPOSEIN.

Emilie Le Rhun, MD, PhD[1]

Michael Weller, MD[2]

Marie Cecile Le Deley, MD, PhD[3]

**Affiliations**
1: a: University of Lille, Inserm, U-1192, Lille, France; b: Neuro-oncology, General and Stereotaxic Neurosurgery service, University Hospital of Lille, Lille, France; c: Breast Cancer Department, Oscar Lambret Center, Lille, France; d: Department of Neurology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland
2: Department of Neurology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland
3 a: Department of Biostatistics, Oscar Lambret Center, Lille, France; b: CESP, INSERM, Paris-Sud, Paris-Saclay University, Villejuif, France

**Funding**
None

**Conflicts of interest**
ELR has received honoraria for lectures or advisory board from Tocagen, Abbvie, Daiichy Sankyo.
MW has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD) and Novocure, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Medac, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen.
MCLD has nothing to disclose.

**References**

1. Le Rhun E, Wallet J, Mailliez A, et al. Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for newly diagnosed leptomeningeal metastasis from breast cancer. *Neuro-oncology*. 2020;22(4):524-538. doi:10.1093/neuonc/noz201

2. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340. doi:10.1136/bmj.c869

3. Morikawa A, Jordan L, Rozner R, et al. Characteristics and Outcomes of Patients With Breast Cancer With Leptomeningeal Metastasis. *Clin Breast Cancer*. 2017;17(1):23-28. doi:10.1016/j.clbc.2016.07.002